

Amendments to the Specification:

Please amend the application, without prejudice, as follows, where stricken through language or double bracketed structures are being deleted and underlined language or structures are being inserted:

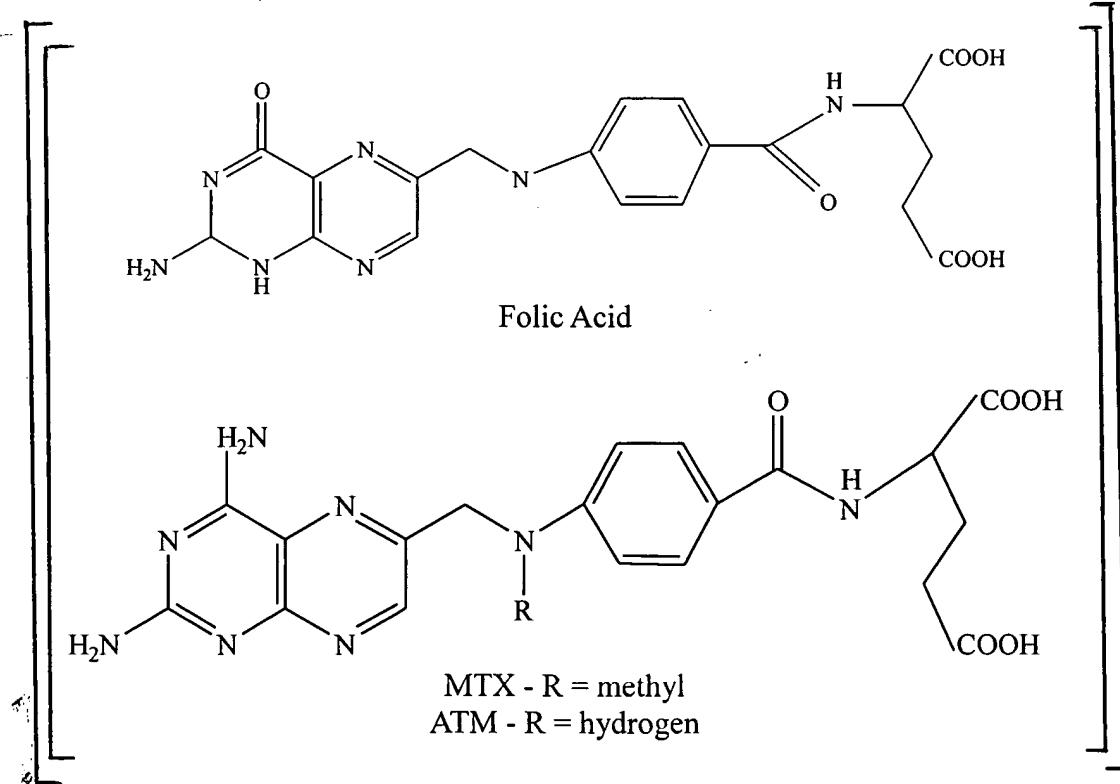
At page 1, line 1, please amend the title as follows:

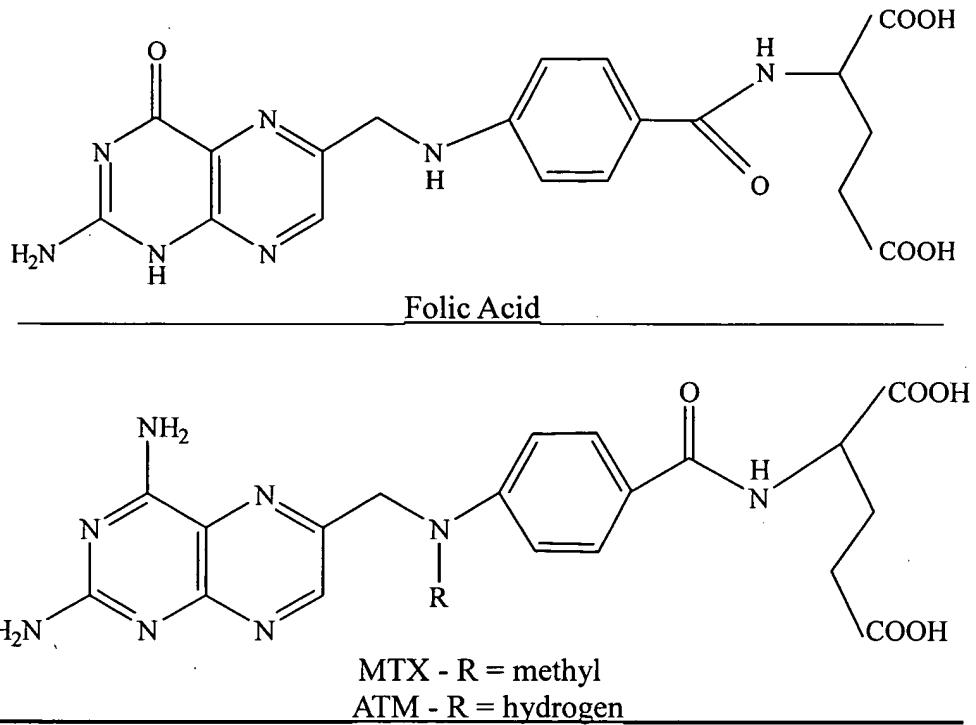
PROCESS FOR SYNTHESIZING 6-QUINAZOLINYL-ETHYL-BENZOYL AND RELATED ANTIFOLATES.

At page 1, lines 5-8, please amend the paragraph as follows:

This invention relates to novel and useful processes for synthesizing compounds that are analogues of ~~λ-methylene-10-deazaaminopterin~~ γ-methylene-10-deazaaminopterin (MDAM), and will have application to the synthesis of certain di- and tri-deaza analogues thereof.

At page 2, please amend the first two structures as follows:





At page 5, lines 1-5, please amend the paragraph as follows:

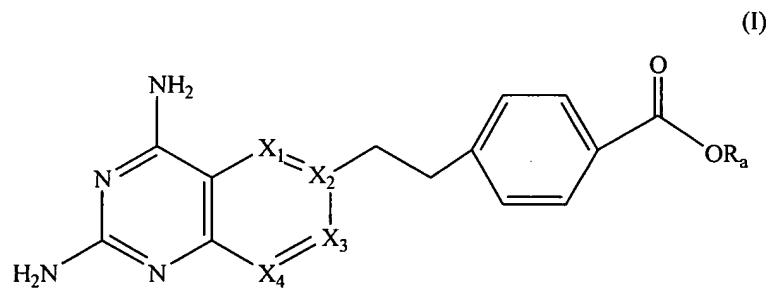
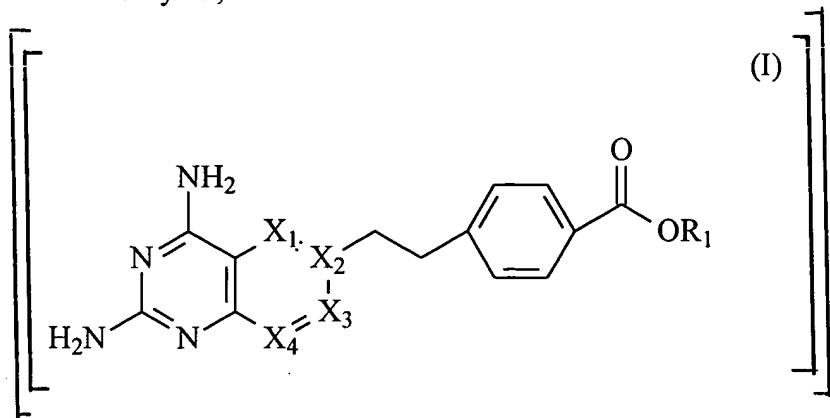
M. G. Nair, US Patent 5,912,251 U.S. Patent 5,912,251 (1999). Another reported synthetic process for making a close analogue of TRIDAM (identical in all respects except for the amino acid residue) was disclosed by ~~Harris, et al. in~~ N.V. Harris, et al., *Synlett.*, No. 4, 577 (1990), and is shown below as Scheme B.

At page 6, line 5, please amend the paragraph as follows:

~~N.V. Harris, et al., *Synlett.*, 577 (October 1990)~~ N.V. Harris, et al., *Synlett.*, No. 4, 577 (1990).

At page 6, lines 13-18, please amend the paragraph as follows:

The critical intermediate synthesized according to the process of this invention is the analogue of pteroic acid, shown below as Formula I.

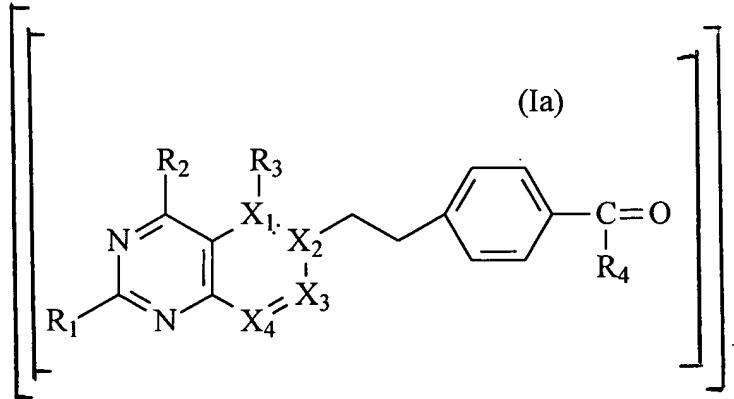


where R_1 , R_a is hydrogen, lower alkyl, or any oxygen protecting group, and X_2 is carbon or nitrogen, and X_1 , X_3 and X_4 are each individually CH or nitrogen.

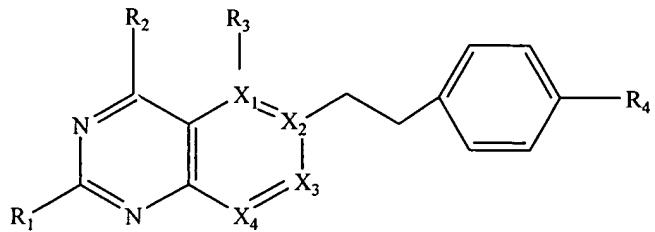
At page 7, line 13, through page 8, line 2, please amend the paragraph as follows:

The process of this invention provides for the synthesis of compounds having the formula

Ia below:



(Ia)



wherein R₁ and R₂ are each individually amino or N-alkyl substituted amino; hydroxy; alkoxy; keto; lower alkyl; or a nitrogen or oxygen protecting group;

R₃ is hydrogen; hydroxy; alkoxy; trifluoromethyl alkoxy; halo; sulfhydryl or alkylthio;

R₄ is hydroxy; alkoxy; or -C(O)-X;

X is hydroxy; alkoxy; or an amino acid residue; and

X₁ and X₂ are each individually carbon or nitrogen, and X₃ and X₄ are each individually CH or nitrogen.

At page 14, lines 1-11, please amend the paragraph as follows:

2,4-diamino-6-nitro quinazoline (40 g, 195 mmole), DMF (320 ml), acetic acid (3.2 ml) and 10% Pd/C (4.0 g) were charged into a ~~1-liter~~ 1-liter flask for Parr Apparatus and hydrogenated under 40 psi overnight. The catalyst was filtered off through Celite. The filtrate was concentrated to about 40 ml under reduced pressure and ethyl acetate (900 ml) was added to the concentrated residue. The resulting suspension was stirred for 30 minutes. The yellow-greenish solid was filtered, washed with fresh ethyl acetate and dried *in vacuo* to yield 30.2 grams of the product. ¹HNMR (DMSO-d₆) δ: 4.82 (bs, 2H), 6.08 (bs, 2H), 6.89-7.97 (m, 3H), 7.11 (bs, 2H).

Please amend the paragraph bridging pages 14 and 15 as follows:

A cold solution of NaNO₂ (23 g, 333 mmole) in water (170 ml) was added to an ice-water bath pre-cooled solution of 2,4,6-triamino quinazoline (57 g, 325 mmole) in 2M HCl (660 ml). The mixture was stirred until it was clear and then added to a warm (50-55 °C) mixture of CuSO₄·5H₂O (82 g, 328 mmole) in water (250 ml) and KCN (106.5 g, 1635 mmole) in water

(190 ml), which were stirred in a ~~5-liter~~ 5-liter four-necked flask equipped with a mechanical stirrer, additional funnel, condenser, nitrogen inlet and gas outlet leading into NaOH solution. The reaction mixture was stirred at 52-55 °C for 30 minutes and then allowed to cool to ~35 °C. Concentrated NH₄OH (325 ml) was added and the mixture was stirred at room temperature for 1 hour. The precipitates were filtered and boiled in 15% acetic acid (875 ml) for 5 minutes. The suspension was filtered while hot. The warm filtrate was diluted with 2-methoxy ethanol (740 ml) and concentrated NH₄OH (265 ml). The resulting suspension was allowed to cool to room temperature and stored in a refrigerator for 4 hours. The precipitate was filtered, washed with cold water and dried *in vacuo* to yield 34.5 g of yellow-greenish product. ¹HNMR (DMSO-d₆) δ: 6.55 (bs, 2H), 7.20 (d, J= 9.0 Hz, 1H), 7.58 (bs, 2H), 7.72 (dd, J= 9.0, 1.8 Hz, 1H), 8.50 (d, J= 1.8 Hz, 1H).

Please amend the paragraph bridging pages 18 and 19 as follows:

The starting material (35 g, 109 mmole), 10% Pd/C (7.0 g) and DMF (700 ml) were charged into a ~~2-liter~~ 2-liter flask for Parr Apparatus and hydrogenated at 20 psi for 20 hours. The completion of the reaction was checked by ¹HNMR. The suspension was filtered through Celite and the filtrate was evaporated to almost dryness under reduced pressure. The residue was stirred in ethyl acetate (700 ml) for 30 minutes. The precipitate was filtered, washed with fresh ethyl acetate and dried under vacuum. The product (32.6 g) was obtained as light yellow solid. ¹HNMR (DMSO-d₆) δ: 2.89-3.01 (m, 4H), 3.83 (s, 3H), 5.97 (bs, 2H), 7.11 (d, J= 8.7 Hz, 1H), 7.24 (bs, 2H), 7.38 (app d, J= 8.4 Hz, 3H), 7.86 (m, 3H).